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Chronic psychosocial and financial burden accelerates 5-year telomere shortening: Findings from the Coronary Artery Risk Development in Young Adults Study

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Abstract

Leukocyte telomere length, a marker of immune system function, is sensitive to exposures such as psychosocial stressors and health-maintaining behaviors. Past research has determined that stress experienced in adulthood is associated with shorter telomere length, but is limited to mostly cross-sectional reports. We test whether repeated reports of chronic psychosocial and financial burden is associated with telomere length change over a 5-year period (Years 15 and 20) from 969 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a longitudinal, population-based cohort, ages 18–30 at time of recruitment in 1985. We further examine whether multisystem resiliency, comprised of social connections, health-maintaining behaviors, and psychological resources, mitigates the effects of burden on telomere attrition over five years. Our results indicate that adults with high chronic burden do not show decreased telomere length over the five-year period. However, these effects do vary by level of resiliency, as regression results revealed a significant interaction between chronic burden and multisystem resiliency. For individuals with high chronic burden and low multisystem resiliency (1SD below the mean), there was a significant 5-year shortening in telomere length, whereas no significant relationships between chronic burden and attrition were evident for those at moderate and higher levels of resiliency. These effects apply similarly across the three components of resiliency. Results imply that interventions should focus on establishing strong social connections,

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psychological resources, and health maintaining behaviors when attempting to ameliorate stress-related decline in telomere length among at-risk individuals.

Introduction

Exposure to life stressors and the experience of chronic psychological stress have been linked to disease development and early mortality.[1–4] While engagement in unhealthy behaviors account for a portion of how stress increases risk for disease and mortality, widespread evidence suggests that prolonged activation of two neurobiological pathways, the sympathetic adrenal medullary pathway and the hypothalamic-pituitary-adrenal axis disrupts effective regulation of immunity and cellular metabolism.[5] Stress-related decrements in immune functioning include impaired wound healing, poorer control of latent viruses and vaccination responses, and elevated states of chronic inflammation.[6] This gradual deterioration of the immune system is partly marked and driven by shortened telomeres, inflammation and oxidative stress.[7,8]

Telomeres are DNA-protein complexes at the ends of chromosomes that protect genes from degradation and oxidative damage, shortening with each cell division. Animal research implicates telomeric shortening in cellular damage and mortality.[9,10] Meta-analytic[11] and Mendelian randomization studies[12] implicate shorter telomeres and common sequence variants of seven telomere-regulating genes with cardiovascular disease pathogenesis. Meta-analyses also associate shorter telomeres cross-sectionally with cancer[13,14] and type 2 diabetes.[15] Other Mendelian randomization studies associate the telomere-regulating common sequence variants with pulmonary[16] and Alzheimer's diseases.[17] Majority of studies,[18–24] with several exceptions,[25–28] further indicate that shorter telomeres predict mortality.[29]

Research demonstrates that exposure to life stressors and reported chronic adult psychological stress[30–35] are associated with shorter telomeres. These studies typically examine specific exposures, such as caregiving, unemployment, and domestic violence, or reported chronic psychological stress, and their relationships to telomere length. These effects were confirmed by a recent systematic review and meta-analysis, demonstrating a small and negative correlation between stress and telomere length.[36] Emerging evidence suggests examining a diversity of exposures to life stressors in adulthood and how they may accumulate to predict short telomeres. Puterman and colleagues recently demonstrated that major life stressors experienced in adulthood accumulate to predict shorter telomeres in nearly 5,000 older adults in a nationally-representative U.S. sample, though these effects were non-significant after adjustment for socioeconomic and behavioral factors.[37] Others have also examined whether stressful life events accumulate to predict shorter telomeres in adults, but within shorter time frames. Verhoeven and colleagues[38] found that increasing numbers of recent stressful life events within the past five years, such as unemployment or financial loss were significantly related to shorter telomeres in Dutch adults.

While these studies suggest an association between accumulated adulthood life stressors and shorter telomeres, they are retrospective accounts of events and thus unable to prospectively establish whether accrual of stressful life events predicts *rate of shortening over time*.

Studies with multiple assessments of telomere length are needed to determine whether accumulation of stressful events promote telomere attrition. To date, one study has examined this question in adults, and demonstrated that greater accumulation of adverse events over the course of a year was significantly associated with accelerated telomere shortening over the same period of time.[39] The current study examines the relationship between reports of chronic psychological and financial burden experienced and the *rate* of telomere attrition over the next five years. Effects were further examined for consistency across race.

Yet, not everyone experiencing chronic burden in adulthood is at equal risk for accelerated telomere shortening, specifically, or disease development, generally. Interest exists in moderating factors that compound or mitigate the effects of chronic burden on disease pathogenesis. While there is considerable focus on genetic polymorphisms that promote differential susceptibilities to environmental factors, a long established basis exists for examining psychosocial and behavioral resources that mitigate the association between chronic stress and telomere attrition. Previous research suggests that psychosocial factors may play a role in dampening the association between stress and health. Psychological resources, including optimism or mastery,[40,41] social connections,[42] and health-maintaining behaviors,[43] have each been shown to mitigate the effects of stress on markers of disease pathogenesis, regardless of whether stress is measured as major life events, chronic burden in response to certain life domains (as measured in the present study), or general chronic psychological stress, as measured by the Perceived Stress Scale.[44] Physical activity has also been demonstrated to moderate the cross-sectional relationship between chronic psychological stress and telomere length[45] and to lengthen telomeres in previously inactive family caregivers reporting high psychological stress randomized to 6 months of aerobic exercise.[46]

While resiliency factors are typically examined independently, recent work proposes that resiliency factors can summate and more effectively mitigate stress effects on health than each factor alone.[47–49] To illustrate, maintaining a physically active lifestyle, in combination with eating and sleeping well, mitigates 1-year telomere attrition associated with adverse life experiences.[39] The use of a multisystem approach (i.e. summing psychosocial and behavioral factors) also moderates the association between depression and shorter telomeres.[50] Thus, in the current study, the independent and combined associations between psychological resources, social connections, and health behaviors with 5-year rate of telomere attrition were tested. We further tested whether these factors mitigate prospective and longitudinal associations between chronic psychosocial and financial burden and 5-year telomere attrition.

Method

Sample

The Coronary Artery Risk Development in Young Adults study (CARDIA; http://www.cardia.dopm.uab.edu/) examines the development and sociodemographic, behavioral, physiological and psychosocial determinants of cardiovascular disease. Data collection started in 1985 with 5,115 healthy black and white participants between 18 and 30 years old. The original cohort was balanced by race, sex, education, and age (see[51] for further

recruitment and procedural information). CARDIA currently includes nine examination periods: 1985–1986 (baseline), 1987–1988 (Y2), 1990–1991 (Y5), 1992–1993 (Y7), 1995–1996 (Y10), 2000–2001 (Y15), 2005–2006 (Y20), 2010–2011 (Y25), and 2015–2016 (Y30).

The present study uses Y15 and Y20 data from a CARDIA ancillary study, *Socioeconomic Status, Stress and Aging*. Seventy-two percent and 69% of the original CARDIA cohort participated in Y15 and Y20. All participants completed blood draws at each year. Participants were selected for the ancillary study if they had stored whole blood available at Y15, Y20 and Y25 (all inclusive, N = 2,480) and had completed tests for coronary artery calcification at all three years (N = 1,258), participants also had to provide permission to utilize blood for DNA studies. A total of 1,002 participants met these criteria and were included in the ancillary study. 969 participants had viable DNA for reliable telomere length estimation. Participants included in this ancillary study, compared to those not in the ancillary, were slightly older at Y15 of CARDIA (40.50 vs 40.06), more likely to be female (65.33% vs. 51.97%), white (59.55% vs. 45.84%), have a higher level of education (2.02 vs.1.96), and were more likely to be non-smokers (18.92% vs 23.14%). non-drinkers (27.45% vs. 17.42%) and heavy drinkers (9.29% vs. 5.40%). Participants included did not differ in body mass index (kg/m^2) or physical activity level from those not included. The University of California San Francisco's institutional review board approved this secondary analysis with de-identified data. Only CARDIA study participants who consented to allow for the use of their stored biological samples in future genetic or molecular studies were included in this study. Table 1 presents the descriptive statistics for the present sample.

Measures

Chronic Burden.—At Y15 and Y20, participants rated whether they were experiencing ongoing difficulties lasting ≥6 months across four life domains (health of close others, work, financial, and relationships), and if so, whether the experience was stressful. Respondents scored each domain on a 4-point scale: '1, None'; '2, Yes, but not very stressful'; '3, Yes, moderately stressful'; and '4, Yes very stressful'. For each domain, responses '1' and '2' were recoded '0' as no or low burden and responses '3' and '4' recoded '1' as moderate or high burden, as done previously[52]. Y15 dichotomized variables across all domains were summed for a Y15 chronic burden exposure score, repeated for Y20, and also summed for a Repeated Chronic Burden score. The composite for each year of assessment ranged from 0 to 4, and for the two repeated years was 0 to 8, with higher scores denoting greater exposure to chronic psychosocial and financial burden.

Psychological Resources.—Taylor and Seeman[40] identified several components of psychological resources that are protective from harmful effects of stress exposures, including optimism, mastery, and emotional regulation, that, in CARDIA, was assessed at Y15 only. These components were assessed, respectively, with the (1) Life Orientation Test-Revised[53] (sample item: "In uncertain times, I usually expect the best"; $\alpha = .78$; 6-items), (2) Pearlin Mastery Scale[54] (sample item: "I have little control over the things that happen to me"; $\alpha = .78$; 7 items), and (3) the Reactive Responding Scale[40] (sample item: "I often respond quickly and emotionally when something happens"; $\alpha = .59$; 9 items), and. All items in all three scales were rated either '1, strongly agree', '2, agree', '3, neutral', '4,

disagree' or '5, strongly disagree', and all scales were scored such that higher scores corresponded to higher levels of the psychological resource. Each scale was then standardized and summed for a total *psychosocial resources* factor. Scores ranged from −8.96 to 6.23.

Social connections.—Two combined scales at Y15 were used[52] to measure the magnitude of participants' sense of social connection, , rated either '1, not at all', '2, a little', '3, some', or '4, a lot'*: family emotional support* (α = .82; 4-items) and *family demands/ burdens* (α = .73; 4-items; reverse-coded). An example item from the family emotional support scale is "How much do members of your family or friends really care about you" and an example item from the family demands/burdens scale is "How often do members of your family or friends make too many demands on you?" Both scales were standardized and summed for a total of *social connections* factor. Higher scores denote a greater sense of social-connectedness. Scores ranged from −7.44 to 2.51.

Health-Maintaining Behaviors.—Two health-maintaining behaviors collected at Y15 were assessed: *Sleep quality* for the last month and total amount of *physical activity* over the past year. Sleep quality was measured with a 1-item question ("During the past month, how would you rate your sleep quality overall?"), on a 5-point scale ranging from (1) very good to (5) very bad and reverse-coded and Z-scored. Participants completed the physical activities history (PAH) questionnaire that measured the frequency and duration of 13 categories of moderate (3 to 4 Metabolic Equivalent units; MET) and vigorous physical activity (≥ 5 METs) over the previous 12 months. Participants recalled number of months of minimal participation in each activity and number of months of specified weekly duration. Total amount of physical activity in Exercise Units (EU) was obtained by multiplying weighted frequency by intensity of activity and summing over all activities. PAH total scores were then standardized and summed with sleep quality score for a total *Health-Maintaining Behaviors* score. Greater values indicate greater engagement in health-maintaining behaviors. Scores ranged from −3.49 to 5.90.

Multisystem Resiliency.—Multisystem resiliency was an averaged composite of standardized health-maintaining behaviors, social connections, and psychological resources, where higher scores denoted greater resiliency. Scores ranged from −9.13 to 5.76. Part-whole correlations for the composite and its respective components (Table 2) indicate the measures were appropriate to composite. The present set of analyses used the individual components (psychological resources, social connections, and health-maintaining behaviors) and the combined multisystem resiliency score in analyses.

Leukocyte Telomere Length.—Leukocyte telomere length (TL) was obtained via banked CARDIA blood samples from years 15 and 20 on 1002 individuals. Specimen were shipped in 96 well plates and housed in a freezer at −80°C at the Blackburn laboratory at UCSF. Blood samples were thawed on the day of the assay and transferred to 384 well plates. The leukocyte TL assay was performed using quantitative PCR methodology adapted from Cawthon[55] and Li and colleagues[56]. Y15 and Y20 samples from the same participant were always plated on the same 96 well plate to avoid batch differences. Each sample was

assayed 3 times on 3 different days. Samples were assayed on duplicate wells, resulting in 6 data points. Sample plates were assayed in groups of three plates, and no two plates were grouped together more than once to eliminate potential systemic plate-to-plate batch differences. Because degraded DNA have high T/S ratios (unpublished results, Blackburn lab), all samples with T/S greater than 1.5 were run on 0.8% agarose gels to assess whether the DNA is degraded. Of the 33 samples run, 10 samples were degraded. These samples were labeled as "DNA degraded" and excluded. In addition, samples with T/S below 0.5 were also run on 0.8% gels. Of the 24 samples run, 4 samples were degraded and were labeled as "DNA degraded" and excluded. The coefficient of variation (CV) for each sample was calculated by dividing the standard deviation (SD) by the average of the six data points. The average CV for all the samples in this study is 3.5%±2.1%.

Telomere T/S ratio was converted to base pairs using the equation: Base Pair (TL) = 3274+(2413*T/S)[56]. Following the conversion to base pairs, a 5-year TL change score was computed: TL change = Base pair TL Y20 – Base pair TL Y15. Negative values of TL change indicate attrition over the five-year period.

Covariates.—Covariates utilized for the present study were collected at Y15 and included: (1) Sociodemographic factors, (2) health risk, and (3) medical history.

Sociodemographic covariates included age, sex, race, education, and household income. Consistent with past research using the CARDIA study,[52] a continuous distribution of household income was created by selecting the midpoint across nine income categories of specific ranges. This new continuous variable was cube-transformed to minimize skew and kurtosis.

Health risk included body mass index (BMI), alcohol use, and smoking history. BMI (weight/height^2) was categorized as underweight (<18.5), normal (18.5–24.9), overweight (25.0–30.0) and obese (>30.0) Alcohol use was categorized as non-drinkers, moderate drinkers (women: 1–10 drinks/week; men: 1–15 drinks/week), and heavy drinkers (women >10 drinks/week; men >15 drinks/week). Smoking history categorized users as non-smokers, current smokers, or past smokers. Medical history was a self-reported summed variable of twenty-one diagnosed chronic physical health conditions.

Statistical Analyses

Analyses were computed in SAS 9.4. Frequencies and descriptive statistics were probed. Following deletion of cases without telomere data, there were missing data on education (.1%), income (.7%), smoking history (.2%), BMI (.2%), and past illness history (4%). Participants missing past illness history (n = 41) had less education than those with past illness data (r = −.06, p =.05). Participants missing data on income (N = 7) were more likely to be male (r = .09, p = .004), be black (r = .10, p = .001), have lower education (r = −.10, p=.002). To handle the missing cases, we utilized multiple imputation and created 25 new datasets with Proc MI; results from the imputed datasets were then pooled with Proc MIanalyze[57,58].

The following analyses were completed for the study. Bivariate correlations between Y15 and Y20 TL measures, chronic burden at Y15 and Y20, and multisystem resiliency and its components were examined. Next, we regressed TL change on chronic burden at Y15 (Model A), without covariates or resiliency factors. Next, we regressed TL change on Y15 chronic burden, and included sociodemographic factors as covariates (Model B). Model C included Model B and health risk factors. Model D included Model C and medical history, and Model E included Model D factors and the independent resiliency factors. We then completed three individual regression analyses that included an interaction term between chronic burden at Y15 and psychosocial resources, social connections, and health-maintaining behaviors, while including the other two resiliency factors as covariates. Next, we repeated these sets of analyses whereby multisystem resiliency replaced the three individual resiliency factors, and completed a final regression that included the interaction between chronic burden at Y15 and multisystem resiliency. These analyses were repeated including the repeated chronic burden score (Y15+Y20) in lieu of the Y15 chronic burden score alone. The Benjamini-Hochberg false discovery adjustment[59] was used to correct for multiple interaction analyses, with significant interaction terms probed. All decomposition models had acceptable multicollinearity diagnostics (VIF >10 and Tolerance <1).

Results

Descriptive and Bivariate Statistics.

At Y15, participants were, on average, 40.50 years old (*SD* = 3.51), white (59.55%), female (65.33%), and college educated (60.43%). Participants were predominantly overweight (35.47%) or obese (32.99%), were mostly non-smokers (62.36%), and moderate drinkers (63%). Forty-six percent (46.44%) of participants reported no somatic ailments, 43.32% reported 1–2 somatic ailments, and 10.24% reported 3+ somatic ailments. Table 1 displays full descriptives, and also by race and sex.

At Y15, mean TL was 5,582 base pairs (*SD* = 466.45). At 5-year follow-up, mean TL was 5,674 base pairs (*SD* = 435.33). TL change over the 5 years was 92.64 (*SD* = 462.58, range −1566.90 to 1650.41), suggesting an average 18.5 base-pair increase in telomere length per year. Leukocyte telomere lengths at Y15 and Y20 were significantly positively associated (r = .48, p <.0001). Y15 TL was negatively associated with TL change (r = −.56, p < .0001). TL change did not differ as a function of sex (p =.66) or race (p =.24).

See Table 2 for correlations between each resiliency factor, multisystem resiliency, chronic burden at Y15 and Y20, and TL Y15, Y20 and change.

Direct Associations of Y15 Chronic Burden and Resiliency Factors with TL Change.

TL change was regressed on chronic burden at Y15, not including any covariates or resiliency factors, and estimates were not significant (B = −0.88, *SE* =12.59, *.95 % CI* = −25.59, 23.83, p = .94) (Table 3, Model A). In a final model (Table 3, Model E) adjusting for sociodemographic factors, health risks, and medical history, chronic burden at Y15 was not significantly associated with TL change (p = .81), nor were psychological resources (p = .15), social connections (p = .36), and health-maintaining behaviors (p = .40). In a separate

fully-adjusted model with individual resiliency factors removed and replaced with the combined multisystem resiliency (individual models not shown), multisystem resiliency was also not significantly related to TL change ($B = -10.60$, $SE = 7.45$, $95\ \%\ CI = -25.23, 4.03$, $p = .16$).

Interactions Between Y15 Chronic Burden and Resiliency Factors with TL Change.

In separate analyses, the interaction between Y15 chronic burden with psychological resources ($B = 9.54$, $SE = 4.78$, $95\%\ CI = 0.16, 18.92$, $p = .046$) was significant, but not for social connections ($B = 7.54$, $SE = 7.05$, $95\ \%\ CI = 6.30, 21.37$, $p = .29$) and health-maintaining behaviors ($B = 16.01$, $SE = 9.02$, $95\ \%\ CI = -1.70, 33.71$, $p = .08$). The interaction term for multisystem was significant ($B = 10.43$, $SE = 5.28$, $95\%\ CI = 0.07, 20.79$, $p = .048$). However, when the Benjamini-Hochberg correction for the false discovery rate (FDR) is applied to these four completed interactions, no interaction remained significant.

Direct Associations of Repeated Chronic Burden (Y15+Y20) and Resiliency Factors with TL Change.

In a model without any covariates, repeated chronic burden was not associated with TL change (Table 4, Model A). Adjusting for all covariates (Table 4, Model E), repeated chronic burden was not significantly associated with TL change ($p = .55$), nor were psychological resources ($p = .14$), social connections ($p = .32$), and health-maintaining behaviors ($p = .42$). In a separate fully-adjusted model (individual models not shown), the combined multisystem resiliency score was not significantly related to TL change ($B = -11.48$, $SE = 7.56$, 95% CI $= -26.37, 3.41$, $p = .13$).

Interactions Between Repeated Chronic Burden (Y15+Y20) and Resiliency Factors with TL Change.

Interactions between repeated chronic burden with psychological resources ($B = 7.85$, $SE = 2.78$, 95% CI = 2.40, 13.30, $p = .005$), social connections ($B = 8.51$, $SE = 4.08$, 95% CI = 0.52, 16.51, $p = .04$), health-maintaining behaviors ($B = 11.97$, $SE = 5.26$, 95% CI = 1.64, 22.29, $p = .02$) were all significant. The interaction between repeated chronic burden and multisystem resiliency was also significant ($B = 8.82$, $SE = 3.01$, 95% CI = 2.90, 14.73, $p = .004$). Accounting for the FDR for multiple testing, each resiliency factor significantly moderated the relationship between repeated chronic burden and telomere length change (Standardized β range 0.12 to 0.16; p's $< .05$). Table 4 summarizes the simple slope analyses for the associations between Y15+20 chronic burden and TL change at the means of each resiliency factor examined, and at 1SD above and below the means. As seen in Table 5, at lower levels of multisystem resiliency, repeated chronic burden was significantly associated with accelerated telomere attrition, whereas unrelated to telomere attrition at mean or higher levels of resiliency. Similar trends in effects were observed for the three independent resiliency factors, but repeated chronic burden was only associated with significant telomere attrition at low levels of psychological resources.

Follow-up analyses revealed that when sleep quality was substituted for average sleep hours per night, analyses yielded similar results. Additional follow-up analyses revealed that the effects presented were not modified by race.

Discussion

This study sought to examine the effects of chronic burden on telomere length change over time, and whether telomere change is different at different levels of psychosocial and behavioral resiliency factors. Results show that individuals with decrements of psychosocial and behavioral resiliency have significant declines in telomere length over five years that are directly associated with their repeated reports of chronic burden across multiple domains, whether examined prospectively or with repeated assessments at the 5 year intervals. The compounding effect between decrements of resiliency and chronic burden was especially robust when we examined repeated reports of chronic burden, as these effects remained significant after adjustment for the false discovery rate. Conversely, participant 5-year telomere length change was unrelated to their repeated reported chronic burden for those with average or higher resiliency. Findings were consistent whether psychosocial and behavioral factors were considered independently or combined into a multisystem resiliency factor. These findings are similar to previous cross-sectional studies indicating that behavioral and psychosocial factors combine to mitigate the association between chronic stress[45] or depression[50] and telomere length cross-sectionally and between psychosocial stressors and telomere attrition over a one-year period.[39]

Psychosocial, socioeconomic, and environmental stressors in adulthood and reports of chronic psychological stress have been implicated in accelerating systemic physiological deterioration among individuals, as discussed in the allostatic load model[60] and weathering hypothesis.[61] Elevated levels of the stress hormone, cortisol, have been associated with shorter telomeres,[62,63] with some exceptions.[64] Steptoe and colleagues[65] have demonstrated that individuals who increased their cortisol levels by ≥20% in response to mental stress had shorter telomeres three years later, compared to those who did not have elevated cortisol levels, after covarying for sociodemographic and health factors. The current study considered a chronic difficulty as psychologically stressful only if participants reported that the stressors were at least moderately or very stressful. Similarly, daily stressors and their related changes in affective states are prospectively impactful on psychological[66] and physical health[67] and mortality[68] in individuals who affectively react more to the stressors compared to those who react less. Taken together, these studies suggest that proximal affective, cognitive, and biological responses to stressors may have long-term effects on health outcomes and early mortality. However, future studies should clarify the independent roles of stressor exposure and the perceptions of stress in the face of these stressors on health and mortality, as has been proposed elsewhere.[69]

Our results indicate that these conclusions may be true, but perhaps only in those with insufficient resiliency, and only in those who report burden repeatedly. Here, only those participants with low levels of psychological and social resources and who were less likely to maintain healthful behaviors had significant telomeric attrition associated with chronic psychosocial and financial burden reported twice over a 5-year period. Psychosocial

resources and healthy behaviors have been proposed elsewhere as inoculating individuals to stress,[42,47,70,71] suggesting that these factors act to mitigate or buffer against life stressors and lifespan adversity. However, psychosocial resources and engagement in more, compared to less, healthful behaviors emerge through the repeated experience with adversity across the lifespan, especially in childhood, as proposed by the environmental affordances model[72] or biographical structuration,[73] suggesting mediation. In the current study, it is not surprising then that chronic burden was negatively and significantly associated with resiliency factors, but these factors were not directly associated with telomere length change. Our study indicates that, even though those repeatedly reporting stressors as stressful are less likely to report having psychosocial resources and maintaining healthful behaviors, the interaction effects suggest that some participants were still resilient in the face of high stress perceptions, and that these resiliency factors mitigate telomere length change. Future studies are required that repeatedly assess psychosocial and financial stressors and assessments of social connections, psychological resources, and health-maintaining behaviors across the lifespan to disentangle who emerges resilient in the face of stressors and what environmental conditions allow for resiliency to develop.

The current study has several strengths. First, measures of chronic burden were evaluated at two consecutive time points separated by 5 years, used with corresponding leukocyte telomere lengths assayed from extracted DNA from stored frozen blood from Y15 and Y20 of the CARDIA Study. Previous studies associating psychological stress or life stressors with telomere length were predominantly cross-sectional in nature[70]. Studies that have examined long-term effects of stress on telomere lengths have combined retrospective reports of lifespan stressors and associated them with a one-time measure of telomere length.[37,38,74,75] Prior to the current study, only one study used two assessments of telomere length separated by one year to assess telomere attrition as it corresponds to cumulative exposure to psychosocial and financial stressors.[39] To our knowledge, our study captures the longest period of time between two assessments of telomere length reported in a study examining the prospective relationship between chronic burden and 5-year change in telomere lengths and repeated experiences of chronic burden on accelerated telomere change. While studies with multiple time points are costlier and a greater burden on participants due to the requirement of their repeated participation in study protocols, they provide the opportunity to reveal associations between measures as real life circumstances unfold - associations that cross-sectional studies cannot uncover. Specifically, our study allowed for the discovery of temporal effects between stressful life experiences and resiliency factors, findings that can potentially inform future research and health programs directed to reducing the negative impact of chronic burden.

We next consider study limitations. First, and importantly, there was a slight average annual increase in telomere lengths by approximately 18 bp/year, a departure from some previous studies that indicate that telomere lengths shorten over time, on average. Some studies demonstrate that telomere length is dynamic, with the possibility of lengthening over time, though there is wide debate in the literature about whether telomeres can actually lengthen over time.[76–78] In the CARDIA study, whole blood samples were collected with the same protocols and the same type of genomic DNA extraction kit was used to extract DNA, but different lots were used in both procedures. Telomere length assays for Y15 and Y20 DNA

were completed at the same time, with Y15 and Y20 samples from the same individual on the same plate, circumventing major criticisms suggesting serious measurement errors when telomere lengths are assayed at different times and on different plates.[79] Previously reported results[80,81] with the CARDIA study telomere data indicated that telomere lengths at Y15 was significantly correlated to telomere lengths Y20 ($r = 0.48$, $p < .001$; reported here as well), and that associations between age, sex and race with telomere lengths at Y15 and Y20 were similar, supporting validity of the values. However, average telomere length at Y15 was lower, suggesting steady DNA degradation. Pre-analytical factors (such as different lots of the blood collection tubes and DNA extraction kits) and length of time blood samples were stored in the freezer may have accounted for the slight upward tick in telomere length.

Second, our study is limited by the time points at which the resiliency factors were measured and their time frames. While physical activity, sleep and social connections were available for Y15 and Y20 of CARDIA (Y15 to Y20 r's= .63, .35, .58 respectively, all p's < .001), none of the psychological resources scales were included more than once, available only at Y15. Given the moderate to strong correlations between Y15 and Y20 for available data and in order to test a multisystem resiliency model that included psychological, behavioral and social components, as we and others have proposed elsewhere[47,70], we designed our study using data available in CARDIA at Y15 to develop our resiliency measures. Subjective sleep and physical activity assessments were used to develop a health-maintaining behaviors measure and were measured on different time frames. Previous CARDIA[82] research reported over-reporting of sleep duration through self-report when compared to sleep duration measured by actigraphy devices. Self-reported physical activity is also known to be over-reported in retrospective reports.[83] Objective measures of either behavior were unavailable at Y15 and thus unavailable to test whether objective measures of health behaviors would display similar mitigating effects. Furthermore, dietary behaviors have also been evidenced to either mitigate[39] or compound[84] the effects of chronic stress on health outcomes. Health-maintaining behaviors naturally cluster[85,86] and, in combination, are associated with longer telomeres than each behavior alone.[87] Diet, physical activity and sleep quality combine to significantly mitigate telomere attrition in those reporting greater adversity over a one year period whereas each behavior alone only trended towards significance.[39] Dietary patterns were unavailable at Y15.

Repeated psychosocial, work-related, and economic stressors that were experienced as stressful were related to accelerated telomere attrition over a 5-year period *only* in midlife adults who reported low levels of psychosocial and behavioral resiliency. These results add to a growing literature on both the health burden of long-term stress and the importance of maintaining healthy social connections, emotion regulation and behaviors as we age. Importantly, the current results suggest that future intervention and policy may benefit from identifying and targeting individuals with appraisal phenotypes most stress-susceptible and designing approaches to alter these appraisals, creating and promoting stable, social communities for vulnerable individuals, and developing community-based approaches to support healthy behavior engagement during times of stress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Means and frequencies of predictors and covariates, prior to imputation.

		Race		Sex	
	Total Sample	**Black**	**White**	**Male**	**Female**
	(N = 969)	(N = 392)	(N = 577)	(N = 336)	(N = 633)
Age in Years, M (SD)	40.5 (3.59)	39.72 (3.86)	41.04 (3.30)*	40.40 (3.52)	40.56 (3.63)
Telomere Length at Y15 (in BP)	5581.50 (466.45)	5625.85 (455.48)	5551.37 (471.78)*	5553.50 (486.26)	5596.37 (455.28)
Telomere Length at Y20 (in BP)	5674.14 (435.33)	5740.42 (454.66)	5629.11 (416.10)*	5637.16 (445.64)	5693.77 (428.81)
Telomere Length Difference Score	92.64 (462.58)	114.57 (459.56)	77.74 (464.43)	83.66 (476.33)	97.40 (455.42)
Income	2.22 (0.06)	2.20 (0.06)	2.24 (0.04)*	2.23 (0.04)	2.21 (0.06)*
Sex, %					
Female	65.33	74.74	58.93*	-	-
Male	34.67	25.26	41.07	-	-
Race,%					
White	59.55	-	-	70.54	53.71
Black	40.45	-	-	29.46	46.29
Education,%					
Completed High School or less	18.60	25.32	14.04*	20.00	17.85
Completed High School and College	60.43	66.50	56.33	58.51	61.45
Some Post-College Education	20.97	8.18	29.64	21.49	20.7
Body Mass Index, %					
Underweight (<18.5)	1.34	1.79	1.04*	0.60	1.74*
Normal (18.5–24.9)	30.20	17.65	38.72	26.49	32.17
Overweight (25.0–30.0)	35.47	34.78	35.94	47.32	29.16
Obese(>30.0)	32.99	45.78	24.31	25.60	36.93
Smoking status, %					
Non-Smoker	62.36	64.45	60.94*	66.96	59.9
Former Smoker	18.72	11.76	23.44	15.77	20.29
Current Smoker	18.92	23.79	15.63	17.26	19.81

		Race		Sex	
	Total Sample	**Black**	**White**	**Male**	**Female**
Drinking Status, %					
Non-Drinker	27.45	30.36	25.48	19.05	31.91*
Moderate Drinker	63.26	62.24	63.95	69.35	60.03
Heavy Drinker	9.29	7.40	10.57	11.61	8.06
Chronic Disease, M (SD)	0.92 (1.15)	1.05 (1.31)	0.84 (1.01)*	0.62 (0.88)	1.08 (1.24)*
Multisystem Resiliency					
Multi-System Resiliency	0.00 (2.23)	−0.34 (2.36)	0.23 (2.10)*	0.47 (2.07)	−0.25 (2.27)*
Social Connections	0.00 (1.65)	−0.26 (1.79)	0.18 (1.53)*	0.19 (1.48)	−0.10 (1.73)*
Psychological Resources	0.00 (2.44)	−0.01 (2.49)	0.01 (2.42)	0.18 (2.28)	−0.09 (2.52)
Health-Maintaining Behaviors	0.00 (1.47)	−0.26 (1.50)	0.18 (1.41)*	0.41 (1.51)	−0.22(1.39)*
Demands	2.04 (0.63)	2.13 (0.67)	1.98 (0.59)*	1.91 (0.57)	2.11 (0.64)*
Emotional Support	3.55 (0.53)	3.49 (0.59)	3.59 (0.49)*	3.54 (0.49)	3.55 (0.56)
Optimism	3.85 (0.58)	3.82 (0.58)	3.86 (0.58)	3.82 (0.56)	3.86 (0.59)
Non-Reactivity	3.44 (0.44)	3.42 (0.44)	3.45 (0.45)	3.52 (0.41)	3.39 (0.45)*
Mastery	4.13 (0.58)	4.17 (0.60)	4.11 (0.56)	4.16 (0.54)	4.12 (0.59)
Sleep Quality	3.52 (1.01)	3.44 (1.02)	3.58 (1.00)*	3.56 (0.94)	3.50 (1.04)
Total Exercise	333.56 (271.77)	284.12 (269.81)	367.06 (268.18)*	433.23 (292.65)	632.00 (280.57)*
Chronic Burden					
Chronic Burden Y15+Y20, M (SD)	2.49 (2.03)	2.41 (2.07)	2.54 (2.00)	2.06 (1.83)	2.71 (2.09)*
Chronic Burden Y15, M (SD)	1.20 (1.18)	1.10 (1.17)	1.27 (1.19)*	1.00 (1.07)	1.31 (1.22)*
Chronic Burden Y20, M (SD)	1.30 (1.21)	1.34 (1.30)	1.27 (1.15)	1.07 (1.10)	1.42 (1.25)*

*$p < .05$

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Table 2.

Bivariate Correlations between Multisystem Resiliency, Components, and its Measures.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Multisystem Resiliency	--													
2. Social Connections	.77**	--												
3. Psychological Resources	.78**	.46**	--											
4. Health-Maintaining	.68**	.25**	.27**	--										
5. Demands	−.62**	-.83**	−.35**	−.21**	--									
6. Emotional Support	.65**	.83**	.42**	.20**	−.37**	--								
7. Optimism	.68**	.40**	.85**	.26**	−.27**	.39**	--							
8. Non-Reactivity	.59**	.32**	.78**	.22**	−.27**	.27**	.50**	--						
9. Mastery	.64**	.41**	.81**	.20**	−.32**	.36**	.58**	.40**	--					
10. Sleep Quality	.61**	.32**	.30**	.73**	−.27**	.26**	.27**	.22**	.24**	--				
11. Exercise	.39**	.04	.10*	.73**	−.04	.03	.11*	.09*	.05	.07	--			
12. Chronic Burden Y15+20	−.36**	−.33**	−.25**	−.22**	.33**	−.22**	−.18**	−.17**	−.26**	−.27**	−.06	--		
13. Telomere Length at Y15	.03	.02	.06	−.01	−.03	.00	.05	.04	.05	.03	−.04	−.06	--	
14. Telomere Length at Y20	−.01	−.03	.00	−.00	−.00	−.05	−.00	.00	.00	.00	−.00	−.07*	.48**	--
15. Telomere Length Change	−.04	−.05	−.06	.01	.03	−.05	−.05	−.04	−.04	−.03	.04	−.01	−.56**	.46**

NOTE: Shaded correlations correspond to the associations between components and their respective composites in the column.

** p<.001;

* p<.01;

p≥.05;

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Table 3.

Multiple linear regression models examining the association between Y15 chronic burden and five-year telomere change.

Variables	Model A		Model B		Model C		Model D		Model E	
	B (SE)	95% CI	B (SE)	95% CI	B (SE)	95% CI	B (SE)	95% CI	B (SE)	95% CI
Chronic Burden Y15	−0.88 (12.59)	−25.59, 23.83	0.08 (12.87)	−25.17, 25.33	1.41 (13.03)	−24.16, 26.98	1.74 (13.14)	−24.04, 27.53	−3.29 (13.64)	−30.06, 23.49
Sociodemographics Factors										
Age at Y15	-	-	2.85 (4.24)	−5.47, 11.17	2.89 (4.29)	−5.52, 11.30	2.93 (4.30)	−5.49, 11.36	2.78 (4.29)	−5.65, 11.20
Sex (Female = 0)	-	-	−11.35 (32.44)	−75.01, 52.30	−12.56 (35.50)	−78.29, 53.18	−13.46 (33.81)	−79.81, 52.90	−17.41 (34.09)	−84.32, 49.50
Race (White = 0)	-	-	42.53 (34.05)	−24.29, 109.35	44.48 (35.21)	−24.61, 113.58	44.78 (35.26)	−24.41, 113.97	48.89 (35.66)	−21.09, 118.87
Completed HS and College[a]	-	-	−62.83 (50.89)	−162.70, 37.04	−69.20 (52.34)	−171.91, 33.51	−68.61 (52.45)	−171.53, 34.32	−63.92 (52.46)	−166.87, 39.03
At Least Some Post-College[a]	-	-	−52.32 (40.43)	−131.67, 27.03	−54.11 (41.02)	−134.61, 26.39	−53.87 (41.06)	−134.44, 26.69	−49.66 (41.15)	−130.42, 31.09
Income	-	-	260.55 (305.56)	−339.10, 860.21	231.23 (313.47)	−383.94, 846.41	226.27 (314.59)	−391.10, 843.65	344.50 (319.56)	−282.63, 971.63
Health Risks										
Former Smoker[b]	-	-	-	-	−30.84 (40.36)	−110.05, 48.37	−30.58 (40.40)	−109.87, 48.71	−27.67 (40.42)	−106.99, 51.64
Current Smoker[b]	-	-	-	-	−21.85 (41.47)	−103.23, 59.54	−21.06 (41.68)	−102.85, 60.73	−22.53 (41.75)	−104.45, 59.40
Moderate Drinker[c]	-	-	-	-	6.60 (34.61)	−61.32, 74.51	6.33 (34.65)	−61.66, 74.33	4.15 (34.65)	−63.84, 72.14
Heavy Drinker[c]	-	-	-	-	21.96 (58.21)	−92.27, 136.19	21.27 (58.35)	−93.23, 135.77	13.96 (58.68)	−101.19, 129.10
Underweight[d]	-	-	-	-	24.07 (133.56)	−238.03, 286.17	24.25 (133.64)	−238.02, 286.51	19.93 (134.27)	−243.56, 283.43
Overweight[d]	-	-	-	-	−18.70 (38.11)	−93.50, 56.10	−18.54 (38.14)	−93.39, 56.32	−16.49 (38.19)	−91.44, 58.47
Obese[d]	-	-	-	-	−26.16 (39.67)	−104.01, 51.69	−25.80 (39.73)	−103.77, 52.17	−24.78 (40.11)	−103.50 53.95
Medical Conditions										
Chronic Disease Symptoms	-	-	-	-	-	-	−2.77 (13.76)	−29.77, 24.23	−4.48 (13.88)	−31.72, 22.76

Variables	Model A		Model B		Model C		Model D		Model E	
	B (SE)	**95% CI**	**B (SE)**	**95% CI**	**B (SE)**	**95% CI**	**B (SE)**	**95% CI**	**B (SE)**	**95% CI**
Resiliency Factors										
Social Connections	-	-	-	-	-	-	-	-	−9.84 (10.78)	−31.00, 11.32
Psychological Resources	-	-	-	-	-	-	-	-	−10.43 (7.20)	−24.56, 3.70
Health-Maintaining Behaviors	-	-	-	-	-	-	-	-	9.56 (11.29)	−12.59, 31.71

[a]referent = no High School Diploma;

[b]referent = Never Smoked;

[c]referent = Non-Drinker;

[d]referent = Normal Weight

Model A = Chronic burden Y15 only

Model B = Model A + sociodemographic factors

Model C = Model B + health risk factors

Model D = Model C + chronic disease symptoms

Model E = Model D + independent resiliency factors

Note: This model was multiply imputed. Bold B denotes statistical significance.

Table 4.

Multiple linear regression models examining the association between Y15+20 chronic burden and five-year telomere change.

Factor	Model A		Model B		Model C		Model D		Model E	
	B (SE)	95% CI	B (SE)	95% CI	B (SE)	95% CI	B (SE)	95% CI	B (SE)	95% CI
Chronic Burden Y15+Y20	−2.05 (7.33)	−16.44, 12.34	−1.67 (7.50)	−16.39, 13.05	−0.85 (7.61)	−15.78, 14.07	−0.66 (7.70)	−15.76, 14.44	−4.85 (8.15)	−20.83, 11.14
Sociodemographics Factors										
Age at Y15	-	-	2.84 (4.24)	−5.47, 11.16	2.88 (4.29)	−5.54, 11.29	2.92 (4.30)	−5.51, 11.35	2.69 (4.29)	−5.73, 11.12
Sex (Female= 0)	-	-	−12.40 (32.53)	−76.25, 51.44	−13.47 (33.61)	−79.43, 52.49	−14.21 (33.90)	−80.73, 52.32	−18.81 (34.16)	−85.85, 48.23
Race (White = 0)	-	-	41.77 (33.93)	−24.81, 108.36	43.67 (35.09)	−25.20, 112.54	43.91 (35.14)	−25.06, 112.88	47.79 (35.53)	−21.93, 117.51
Completed HS and College[a]	-	-	−62.88 (50.88)	−167.72, 36.97	−69.09 (52.35)	−171.82, 33.64	−68.61 (52.45)	−171.54, 34.32	−63.27 (52.46)	−166.23, 39.69
At Least Some Post-College[a]	-	-	−52.28 (40.43)	−131.63, 27.07	−54.02 (41.02)	−134.52, 26.48	−53.83 (41.06)	−134.40, 26.74	−49.04 (41.16)	−129.81, 31.73
Income	-	-	252.00 (305.68)	−347.88, 851.88	224.28 (313.43)	−390.83, 839.39	220.16 (314.51)	−397.07, 837.38	342.28 (319.33)	−284.40, 968.95
Health Risks										
Former Smoker[b]	-	-	-	-	−30.03 (40.42)	−109.35, 49.30	−29.84 (40.46)	−109.23, 49.56	−26.23 (40.46)	−105.64, 53.18
Current Smoker[b]	-	-	-	-	−21.13 (41.44)	−102.45, 60.19	−20.46 (41.65)	−102.19, 61.27	−22.15 (41.71)	−104.01, 59.71
Moderate Drinker[c]	-	-	-	-	6.23 (34.55)	−61.57, 74.03	5.98 (34.60)	−61.91, 73.88	4.20 (34.59)	−63.68, 72.08
Heavy Drinker[c]	-	-	-	-	22.55 (58.25)	−92.06, 136.56	21.61 (58.41)	−93.01, 136.23	15.71 (58.75)	−99.59, 131.02
Underweight[d]	-	-	-	-	24.25 (133.61)	−237.29, 287.11	25.01 (133.69)	−237.34, 287.37	21.17 (134.26)	−242.32, 284.66
Overweight[d]	-	-	-	-	−18.28 (38.14)	−93.13, 56.56	−18.16 (38.16)	−93.06, 56.73	−15.82 (38.82)	−90.80, 59.16
Obese[d]	-	-	-	-	−25.73 (39.71)	−103.67, 52.20	−25.45 (39.77)	−103.50, 52.59	−24.21 (40.12)	−102.94, 54.53
Medical Conditions										
Chronic Disease Symptoms	-	-	-	-	-	-	−2.38 (13.80)	−29.46, 24.71	−3.93 (13.90)	−31.21, 23.35
Resiliency Factors										
Social Connections	-	-	-	-	-	-	-	-	−10.81 (10.88)	−32.16, 10.54
Psychological Resources	-	-	-	-	-	-	-	-	−10.66 (7.21)	−24.81, 3.49
Health-Maintaining Behaviors	-	-	-	-	-	-	-	-	9.06 (11.30)	−13.11, 31.23

[a] referent = no High School Diploma;

[b] referent = Never Smoked;

[c] referent = Non-Drinker;

[d] referent = Normal Weight

Model A = Chronic burden Y15+Y20 only

Model B = Model A + sociodemographic factors

Model C = Model B + health risk Factors

Model D = Model C + chronic disease symptoms

Model E = Model D + independent resiliency factors

Note: This model was multiply imputed. Bold B denotes statistical significance.

Table 5.

Simple Slope analyses for the association between chronic burden and five-year telomere length change as a function of different levels of multisystem resiliency and its components.

	Health-Maintaining Behaviors				Social Connections				Psychological Resources				Multisystem Resiliency		
	B	*95% Confidence Intervals*	*p*		*B*	*95% Confidence Intervals*	*p*		*B*	*95% Confidence Intervals*	*p*		*B*	*95% Confidence Intervals*	*p*
YEAR 15+Y20 Chronic Burden Predicting Telomere Length Change															
−1 SD	−20.00	−40.92, 0.93	.06		−16.66	−36.39, 3.08	.10		−20.43	−39.92, −0.95	.04		−20.07	−39.22, −0.92	.04
Mean	−2.46	−18.56, 13.64	.76		−2.58	−18.69, 13.54	.75		−1.25	−17.39, 14.89	.88		−0.41	−16.54, 15.72	.96
+1 SD	15.08	−8.13, 38.29	.20		11.51	−10.40, 33.41	.30		17.93	−4.33, 40.20	.11		19.25	−3.15, 41.64	.09

Note: The models were multiply imputed.